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DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
LANDAU, SHARMILA GOLLAMUDI	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/435,576
Filing Date: November 08, 1999
Appellant(s): CHEN ET AL.

Robert J. Paradiso
Registration No 41,240
For Appellant

EXAMINER'S ANSWER
(The Examiner's Answer mailed May 24, 2007 is hereby vacated)

This is in response to the appeal brief filed March 5, 2007 appealing from the Office action mailed November 11, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Cheng et al. "Evaluation of Sustained/Controlled Release Dosage Forms of 3- Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors in Dogs and Humans" Pharmaceutical Research (1993), no. 10, pp. 1683-1687.

Remington's Pharmaceutical Science, 18th Edition, 1990.

5,376,383	ALBERTS et al	12-94
5,837,379	CHEN et al	11-98
6,485,748	CHEN et al	11-02

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

A) Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 are rejected under 35 U.S.C. 102(b) as being anticipated by Alberts et al (5,376,383).

Alberts discloses a method of lowering plasma cholesterol levels by administering to a subject a time-controlled drug-delivery device containing a water-soluble HMG-CoA reductase inhibitor (lovastatin, pravastatin, etc) over 6 to 24 hour period. See column 2, lines 54-67. Alberts discloses that using a sustained or controlled release provides for a single dose to yield an equivalent or improved effect as that of a rapid release formulation (col. 1, lines 39-50 and abstract). Example 10 provides a release over 18 hours. Albert discloses a drug delivery device which comprises a core composition comprising (a) a diffusible water soluble HMG-CoA reductase inhibitor, and (b) an osmotically effective agent surrounded by either (a) a water insoluble wall prepared from (i) a polymer material that is permeable to water but substantially

impermeable to solute and (ii) 0.1 to 75% by weight, based on the total weight of (i) and (ii), of at least one water leachable pore forming additive dispersed throughout said wall; or (b) a substantially imperforate water insoluble wall surrounding said core composition and prepared from a semipermeable material substantially impermeable to core composition and permeable to the passage of an external fluid in the environment of use, with said wall (b) having a means for release of the therapeutic agent through the water insoluble wall. See column 3, lines 5-24. Additionally, the formulation lowers the amount of peak drug plasma concentration in the blood; thus the potential side effects of the drug are reduced. The controlled release is over a 6 to 24 hour period (col. 2, line 63). Alberts discloses that this controlled release can be achieved by a variety of procedures known to those skilled in the art and discloses various controlled released matrices in the examples. The procedures suitable for the invention are diffusion-controlled systems, osmotic devices, dissolution controlled matrices, and erodible/degradable matrices (col. 3, lines 1-2). Lastly it should be noted that lovastatin hydrolyzes in vivo to form its acid form, lovastatin acid. The examples provide a controlled device comprising a core and coat, which is substantially similar to instant disclosure Table 1's general formula.

* Note that although the prior art does not explicitly state the instant functional limitations, it is the examiner's position that the instant functional limitation is inherent since Albert's discloses a controlled release rate over an 18-hour period wherein the tablets is substantially similar to Table 1. Thus, the Tmax would inherently fall within instant range. The recitation of a newly discovered function inherently possessed by the prior art, does not make distinguish it form the prior art. Further, it is the applicant's burden to prove otherwise. See In re Best, 195 USPQ 430 (CCPA 1977).

B) Claims 1-13,18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over US patent 5,837,379 to Chen et al by itself or in view of Cheng et al (Evaluation of Sustained/Controlled Release dosage forms of 3-Hydroxy-3-Methylglutaryl-Coenzyme A(HMG-CoA) Reductase Inhibitors in Dogs and Humans, Pharmaceutical Research (1993), 10:1683-1687).

Chen et al disclose a once daily pharmaceutical tablet having a 1) compressed core contains a medicament, a water-soluble osmotic compound, and one or more osmotic polymers, and 2) a membrane coating containing a water insoluble pharmaceutically acceptable polymer and an enteric polymer. See abstract. Although nifedipine is exemplified, Chen teaches various water-insoluble medicaments that may be utilized, including instant lovastatin. See column 2, line 64. The composition may additionally have dispersants, lubricants, dyes, and other additives that are conventionally utilized in the art. See column 5, lines 63-65. More specifically, Chen et al teach the medicament granules contain nifedipine, povidone (osmotic polymer), lactose (osmotic agent), and sodium lauryl sulfate (surfactant). The granules are compressed with lactose, Polyox WSR, and Myvaplex and coated with a color coating contains dye, sodium chloride, and water. The color coating is coated with a sustained release coating; followed by an enteric coating containing HPMC phthalate, pore forming agent, talc, and plasticizer. See examples. Lastly it should be noted that lovastatin hydrolyzes in vivo to form its acid form, lovastatin acid.

Chen does not exemplify lovastatin in the controlled release device nor specify the instant functional limitations.

Cheng et al teach controlled release device containing lovastatin and a sustained release matrix for the treatment of hypercholesterolemia. Cheng discloses that lovastatin hydrolyzes in vivo to form its corresponding beta-hydroxyacid, which are potent inhibitors of HMG-CoA reductase. See page 1683. Further, Cheng discloses that the liver, the target organ, more efficiently extracts lovastatin and simvastatin than their corresponding beta-hydroxyacid. Thus, the use of controlled release device allows for an equal or better therapeutic value. Table II teaches the total HMG-CoA reductase inhibitors (lovastatin and its acid form) pharmacokinetic parameters (AUC, the Cmax, Tmax, AUC ratio of 0.94, 1.03, 0.43, and 0.52, and Cmax ratio of 0.66, 0.64, 0.16, and 0.13) in dogs receiving various lovastatin dosage forms. See page 1685. Table V teaches the pharmacokinetics of simvastatin administered to humans. CRS14 formulation provides for a **Tmax of 7.5 + 1.2 hours (standard deviation 8.7 hours and Appellant claims about 10 hours)** for an 80mg lovastatin oral dose. See page 1687.

It is deemed obvious to one of ordinary skill in the art at the time the invention was made to look to the guidance provided by Chen et al and include the instant lovastatin in the controlled release dosage form. One would have been motivated to do so since Chen teaches a variety of medicaments that would benefit from the use of the instant controlled release formulation and teaches the instant active as one of the suitable medicaments. Therefore, one could reasonably expect similar results by including lovastatin in Chen's controlled release device.

With regard to the instantly claimed Tmax and functional limitations, it is the examiner's position that Chen's controlled release device would meet the instant functional limitations since Chen's controlled release device is substantially similar in structure and formulation to applicant's dosage form described in the specification; in particular note Table I of instant

specification wherein applicant's teaches the general formula of Table I provides the functional limitation. It is noted that the applicant does not claim the controlled release structure in the claims and thus the examiner is permitted to look to the instant specification to define the controlled release device in terms of structure that provides the instantly claimed functional limitations. Therefore, it is the examiner's position that both would function similarly if not the same since the structures of the instant invention and that of the prior art are the same.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further look at Cheng et al and specifically utilize lovastatin in Chen's controlled release device. One would have been motivated to do so since Cheng teaches lovastatin is an effective drug in reducing cholesterol serum levels in humans and it is beneficial to utilize a controlled or sustained release device. Therefore, Cheng provide a further motivation to specifically utilize lovastatin as the drug of choice if one desired to treat cholesterol serum levels. Further, although Cheng utilizes an animal model for drawing the conclusions that controlled release devices provide a better efficacy of lovastatin, it is conventional in the pharmaceutical research to draw conclusions from animal models and apply them to humans.

C) Claims 1-13, 18, 19, 21, 22, 25-47, 76-77, and 80 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,485,748 in view of Remington's Pharmaceutical Science (18th edition, 1990). Although the conflicting claims are not identical, they are not patentably distinct from each other because since they encompass similar subject matter.

Instant application is directed to a controlled release oral solid dosage form for the reduction of serum cholesterol levels containing lovastatin and a controlled release carrier

wherein the said dosage form has certain functional limitations upon consumption of the said dosage form.

US '748 is directed to a controlled release oral solid dosage form containing a compressed core with a slightly soluble to practically insoluble in water medicament and a membrane coating. The specification defines lovastatin as a drug that as a soluble.

Lovastatin is defined as a water-insoluble drug and sparingly soluble in alcohol in Remington's Pharmaceutical Sciences. See page 857-858.

Although US patent does not claim the functional limitation as seen in instant application, the controlled dosage form of US patent '595 would function in a similar manner as instantly claimed dosage form since both claim the same drug and the same controlled release structure. Although US patent '748 recites a generic slightly water-soluble drug to practically insoluble drug, the specification defines lovastatin as a drug that falls within this category. Further, Remington's Pharmaceutical Sciences defines lovastatin as a water-insoluble drug. Thus, the instant application and US patents are related genus-species, wherein instant application recites the species and the species falls within the generic scope of the US patent '748 wherein the specification defines lovastatin as a water-insoluble drug.

(10) Response to Argument

A) Claims 1-13, 18-19, 21-22, 25-29, 31-54, 57-71 and 76-81 are rejected under 35 U.S.C. 102(b) as being anticipated by Alberts et al (5,376,383).

Applicant argues that Lescol is a once a day controlled release dosage form of fluvastatin and has a Tmax of 2.5 to 3 hours and thus not all controlled release dosage form comprising hydroxyl substituted naphthalene will inherently have the instant Tmax. Appellant argues that

the relevance of Lescol is that the examiner has erroneously concluded that any controlled release device comprising an alkyl ester of hydroxy substituted naphthalenes will provide the instant Tmax values. Thus, appellant has submitted the Lescol XL product sheet to demonstrate that the examiner's position is incorrect.

Appellant's arguments are not persuasive for the following reasons:

The examiner, for the record, clarifies that it is not the position of the examiner that any controlled release device comprising HMG-CoA Reductase Inhibitors will provide the instant pharmacokinetics. Rather, it is the examiner's position that since the prior art's controlled release device and appellant's controlled release device are substantially similar, the prior art will have a similar, if not the same, pharmacokinetics. Therefore, the pharmacokinetics of Lescol is irrelevant since it is not the examiner's position that any controlled release device provides the claimed Tmax.

Appellant argues that the examiner has not met the burden of proving inherency and "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation." Applicant argues that Alberts does not inherently provide the instant Tmax and inherency requires that the Tmax must be necessarily present.

The examiner recognizes that inherency requires that an element must be necessarily be present; however "the Patent Office can require the applicant to prove that a subject matter shown in the prior art does not possess a characteristic when there is reason to believe that the functional limitation asserted to be critical in establishing novelty in the claimed subject matter is possessed by the prior art." *In re Best*, 195 USPQ 430 (CCPA 1977). The examiner

acknowledges that the *initial* burden is on the examiner to provide a rationale for inherency; however the examiner respectfully submits this burden shifts to the Appellant to rebut the examiner's position with evidence once a reasonably rationale has been made. Moreover, since the United States Patent Office does not have the capabilities or the facilities to test products for inherent features, it is Appellant's burden to rebut the Office's position with evidence that is a comparison of the closest cited prior art. In instant case, the examiner refers to Table 1 in the instant disclosure to provide the rationale. Applicant discloses that the general structure in Table 1 provides the instant functional limitations. A careful look at Table I demonstrates that the instant invention only requires 1) a core and 2) an outer coating. The seal coat, an inner coat, and overcoat are not required since the claimed range encompasses *zero* and zero clearly implies that the coating is not required to provide the instant functional limitation. Therefore, the examiner submits that the instant structure as defined in Table 1 and prior art's structure are substantially similar and both are used for the same purpose, i.e. providing a controlled release of an effective amount of HMG-CoA inhibitor in the blood.

Instant Invention:	**Prior Art Example 10**
Core:	**Core:**
Alkyl ester of a substituted naphthalene 3-20%	Lovastatin (40g) about 15%
Water swellable polymer 10-40%	Klucel LF (4.8g) Methocel K15M (80g) about 32%
Antioxidant 0.001-0.01%	Butylated Hydroxyanisole (0.04g) about 0.015%
Osmotic agents 20-80%	Lactose (75.2g) about 28.6%

Surfactant **0**-5%	
Lubricant 0-5%	Magnesium Stearate (2.4g) about 0.9%
Outer Coating:	Alberts discloses surrounding the core with a water insoluble coat containing at least one pore forming agent (channeling agent) on column 3, lines 30-40.
Blend of Enteric Polymer and Water-insoluble Polymer 0.5-5%	Cellulose acetate
Plasticizers 0-1%	PEG
Channeling Agent 0.2-5%	Sorbitol

According to the MPEP, "A rejection under 35 U.S.C. 102/103 can be made when the prior art product **seems to be identical** except that the prior art is silent as to an inherent characteristic."

Appellant argues that the examiner's position that the controlled release devices are similar or the same is incorrect since Examples 3-7 do not contain a water soluble polymer and Example 8-16, which do contain the polymer do not teach the outer coating.

The examiner respectfully submits that Example 3-7 do contain water swellable polymers. For instance, Example 5 utilizes polyvinylpyrrolidone, a water-soluble polymer. Example 10, utilizes both Klucel and Methocel, which are water swellable polymers. With regard to the coating, the examiner points out that Alberts discloses on column 3, lines 30-40 and claim 1, "a substantially imperforate water insoluble wall surrounding said core composition and

prepared from a semipermeable material substantially impermeable to core composition and permeable to the passage of an external fluid in the environment of use, with said wall (b) having a means for release of the therapeutic agent through the water insoluble wall."

Appellant argues that the instant invention is not limited to the examples or the formulations provided in Table 1. Appellant argues that the instant invention is not limited only to the controlled release formulations disclosed in Table 1; rather the invention is directed to any controlled release device that will exhibit the claimed Tmax parameters.

The examiner acknowledges that Appellant is not limited to the examples disclosed in the instant specification or to the formulations disclosed on Table 1. Appellant broadly claims a controlled release device using functional limitations rather than structural limitations. Since the Patent Office cannot test the devices discloses by the prior art for functional limitations that may be inherent, the examiner must make a reasonable rationale as to why it is the position of the Office that the functional limitation is inherent. The most reasonable method is for the examiner to compare Appellant's preferred structure, which Appellant discloses provides a Tmax of about 10 to about 32 hours, with the prior art's structure. The fact that the prior art is silent to the pharmacokinetics provided by the device does not necessarily mean it does not provide the same pharmacokinetics.

Appellant argues that Albers does not inherently teaches the claimed Tmax parameters as claimed. Appellant submits Gregory A. McClelland, et al., Enhancement of 3-Hydroxy-3-methylglutargl-Coenzyme A (HMG-CoA) Reductase Inhibitor Efficacy Through Administration of a Controlled-Porosity Osmotic Pump Dosage Form, Pharmaceutical Research, Vol. 8., No. 7. 1991, to support this position. Appellant argues that the examiner has admitted the McClelland

structure is similar to Albert's structure. Appellant argues that McClelland demonstrate in vivo data with respect to this formulation in Figure 2 on page 875, which depicts the peak of the plasma/concentration time curve at a time less than 5 hours. Therefore, Appellant has met the burden to prove the instant pharmacokinetic parameters are not inherent.

The examiner acknowledges that if Appellant provides evidence rebutting the Office's position of inherency, then the rejection must be withdrawn. Further, the examiner acknowledges that McClelland's device is similar to the device disclosed in *Example 3* of US '383. However, example 3 has a release *of less than 14 hours* and the examiner's rationale is based on example 10, which has a release *over an 18-hour period* . The examiner respectfully submits that this is the closest comparison since example 10 has a release rate over 18 hours and the core disclosed is similar to the core disclosed in Table 1, page 19 of the instant disclosure. Thus, the examiner respectfully submits that Appellant must provide evidence comparing the closest prior art of record. Example 3's core is not used in the anticipation rejection. This is critical since the Tmax will change according the release of the a core. Thus, a core that releases over a longer time frame, i.e. over 18 hours, will provide a peak concentration (Tmax) later, whereas a core that releases under 14 hours will provide a peak concentration quicker compared to the over 18 hour release core.

For the forgoing reasons, it is the examiner's position that Alberts anticipates the instant invention.

B) Claims 1-13,18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 are rejected under 35 U.S.C. 103(a) as being unpatentable over US patent 5,837,379 to Chen et al by itself or in view of Cheng et al (Evaluation of Sustained/Controlled Release dosage forms of 3-

Hydroxy-3-Methylglutaryl-Coenzyme A(HMG-CoA) Reductase Inhibitors in Dogs and Humans, Pharmaceutical Research (1993), 10:1683-1687).

Appellant argues that Chen et al fail to teach or suggest the instantly claimed formulation comprising an alkyl ester of hydroxy substituted naphthalenes (HMG-CoA Reductase Inhibitors). Appellant argues that the examiner's position that any controlled release device comprising an alkyl ester of hydroxy substituted naphthalenes will provide the instant Tmax values and thus appellant has submitted the Lescol XL product sheet to demonstrate that the examiner's position is incorrect. Appellant argues that Lescol Xl provides a Tmax of 2.5-3 hours of fluvastatin and the instant invention claims a Tmax of 10 to about 32 hours.

Appellant's arguments have been fully considered but they are not persuasive for the following reasons: The examiner, for the record, clarifies that it is not the position of the examiner that any controlled release device comprising HMG-CoA Reductase Inhibitors will provide the instant pharmacokinetic. Rather, it is the examiner's position that since the prior art's controlled release device and appellant's controlled release device are substantially similar, the prior art will have a similar, if not the same, pharmacokinetics. This will be discussed further below. Therefore, the pharmacokinetics of Lescol is irrelevant since it is not the examiner's position that any controlled release device provides the claimed Tmax.

Appellant argues that Chen et al fail to teach, suggest, or hint the Tmax range recited in the instant claims. Appellant argues that Chen's lack of the teaching of a Tmax or recognition of the criticality of the Tmax. Appellant argues that the only in-vivo data provided is directed to nifedipine and not the instant HMG-CoA Reductase Inhibitors.

The examiner respectfully submits that, "There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference." *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Moreover, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." Therefore, the fact that Chen et al have not explicitly disclosed the critically of the Tmax is not a requirement to reject claims under obviousness.

MPEP 2112, section IV requires that an "examiner must provide rationale or evidence tending to show inherency." As set forth in the rejection and summarized below the examiner has done so. The rationale is as follows:

Appellant's discloses that the "preferred" general structure in Table 1 provides the instant functional limitations. A careful look at Table I demonstrates that the instant invention only requires 1) a core and 2) an outer coating. The seal coat, an inner coat, and overcoat are not required since the claimed range encompasses zero and zero clearly implies that the coating is not required to provide the instant functional limitation. The examiner further points to Appellant's disclosure on page 24, lines 10-15:

Further specific controlled release technologies which may be used in conjunction with the present invention include the Assignee's U.S. Pat. Nos. **5,837,379**; 5,34,023; 5,830,503; 5,736,159; 5,728,402; 5,654,005; 5,567,441; 5,558,879; 5,532,275; 5,508,040; 5,472,708; 5,458,888; 5,458,887; and 5,419,917, all of which are hereby incorporated by reference.

Thus, US 5,837,379, to Chen et al, is in fact disclosed by Appellant to be suitable controlled release formulation to be used in the instant invention.

Chen et al teach a substantially similar controlled release device as taught in Table 1 and the inventive examples.

Instant Invention: Table 1 **General Formula**	**Inventive Example 3** **Specific Formula**	**Prior Art Example 2**
Core:	**Core:**	**Core:**
Alkyl ester of a substituted naphthalene 3-20%	Lovastatin 12.14%	Nifedipine 10.5%
Water swellable polymer **10**- 40%	Polyox WSR Coagulant, 4.55% Polyox WSR N 80, 17.76% Polyox (Polyethylene Oxide)	Polyethylene Oxide 10.5%
Antioxidant 0.001-0.01%	BHT 0.03%	-
Osmotic agents 20-80%	Lactose 51.30%	Lactose (75.2g) 45.5%
Surfactant **0**-5%	Sodium Lauryl Sulfate 3.04%	Sodium Lauryl Sulfate 1.9%
Lubricant **0**-5%	Silicone dioxide 0.46% Glyceryl Monostearate 1.82%	-

Seal Coating 0-10	**Seal Coating** Opadry Clear	**Color Coating 4%** See column 8, line 16. Opadry Yellow
Osmotic Agent 0-10	Sodium Chloride	Sodium Chloride
Inner Coating	**Inner Coating**	**Inner Coating**
Enteric Polymer 0-30%	-	-
Anti-Sticking Agent 0-6%	-	-
Plasticizers 0-6%	-	-
Channeling Agent 0-6%	-	-
Outer Coating:	**Outer Coating:**	**Sustained Release Coating (only 2% applied, which reduces the weight % in composition to be similar to instant weight %)**
Blend of Enteric Polymer and Water-insoluble Polymer 0.5-5%	Cellulose Acetate 1.43% Eudragit S 100 0.49%	Cellulose Acetate 60% Eudragit S 100 20%
Plasticizers 0-1%	Triacetin 0.11% PEG 400 0.11%	Triacetin 5% PEG 400 5%
Channeling Agent 0.2-5%	Sugar 0.72%	Sucrose 10%
Overcoat	**Overcoat**	**Enteric Coating (2-5%**

		applied, which reduces the weight % in composition to be similar to instant weight %)
Enteric Polymer 0-30%	HPMC 0.77%	HPMCP 70%
Anti-Sticking Agent 0-6%	Talc 0.30%	Talc 23%
Plasticizers 0-6%	Triacetin 0.12%	Acetyltributyl Citrate 7%
Channeling Agent 0-6%	Sugar 0.30%	Pore Forming Agent 5-25% or 0-30%

The only difference between the Chen's controlled device and the device disclosed in the instant disclosure and examples is: Chen exemplifies nifedipine and Appellant's examples and Table 1 utilize lovastatin. Chen teaches a core containing the drug, a water-swellable polymer, an osmotic agent, and (surfactant) in the disclosed range as recited in Table I. The examiner respectfully points out that although Chen does not teach an antioxidant in the core, the antioxidant does not affect the control release properties of the device. Chen's core is coated with a color coating containing a color and osmotic agent. The prior art's color coat is comparable to Appellant's seal coat. Note that Chen only utilizes 4% of this coat and thus the weight percent is reduced and falls within appellant's disclosed range. Chen then applies a sustained release coating containing enteric polymer (Eudragit S), water insoluble polymer, and a plasticizer. Note that Chen only utilizes 2% of this coat and thus the weight percent is reduced and falls within

appellant's disclosed range in Table I. The prior art's sustained release coat is comparable to Appellant's inner coat. Lastly, the tablet is again coated with an enteric coating polymer containing an enteric polymer, a pore-forming agent (channeling agent), and plasticizer. Note that Chen only utilizes 2-5% of this coat and thus the weight percent is reduced and falls within appellant's disclosed range. Also it should be noted that acetyltributyl citrate and triacetin are both interchangeable plasticizers and Chen also teaches triacetin in other examples. The prior art's enteric coat is comparable to Appellant's overcoat. Therefore, it can be seen that Chen et al's device is substantially identical to the instantly claimed controlled release device. Thus, it is the examiner's position that Chen's controlled release device will necessarily provide the same pharmacokinetics, i.e. the same Tmax claimed. Although the examiner has not provided a detailed comparison of the other inventive examples and the prior art examples, it should be noted that the structures disclosed are also substantially identical.

"Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a **prima facie case of either anticipation or obviousness has been established**. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, **the applicant has the burden of showing that they are not.**" In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." *In re Best,* 562 F.2d at 1255, 195 USPQ at 433.

Therefore, it is respectfully submitted that the examiner has made a sound rationale and the burden has shifted to Appellant to provide evidence rebutting the examiner's position. However, Appellant has not provided *any* evidence rebutting the examiner's position and rather argues that US 5,837,379 does not direct one to utilize HMG-CoA Reductase Inhibitors. This will be fully addressed below. The examiner respectfully emphasizes that evidence is needed to rebut the Office's position since the recited functional limitation is the asserted critical element in establishing novelty. "Mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art; Patent Office can require applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; this burden of proof is applicable to product and process claims reasonably considered as possessing allegedly inherent characteristics." *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Appellant argues that the instant invention is not limited to the examples or the formulations provided in Table 1. Appellant argues that the instant invention is not limited only to the controlled release formulation disclosed in Table 1; rather the invention is directed to any controlled release device that will exhibit the claimed Tmax parameters.

The examiner acknowledges that Appellant is not limited to the examples disclosed in the instant specification or to the formulations disclosed on Table 1. Appellant broadly claims a controlled release device using functional limitations rather than structural limitations. Since the Patent Office cannot test the devices discloses by the prior art for functional limitations that may

be inherent, the examiner must make a reasonable rationale as to why it is the position of the Office that the functional limitation is inherent. The most reasonable method is for the examiner to compare Appellant's preferred structure, which Appellant discloses provides a Tmax of about 10 to about 32 hours, with the prior art's structure. Again the examiner respectfully points out that the instant specification on page 24 discloses US 5,837,379 is controlled release device that provides the instant functional limitations. The fact that the prior art is silent to the pharmacokinetics provided by the device does not necessarily mean it does not provide the same pharmacokinetics.

Appellant argues that Chen does not provide any examples comprising HMG-CoA Reductase Inhibitors. Appellant argues that there is no specific guidance in formulating the controlled release device with the instant HMG-CoA Reductase Inhibitors.

The examiner recognizes that HMG-CoA Reductase Inhibitors are *suggested* and not exemplified. Hence, the examiner makes the rejection under obviousness and not anticipation. It is respectfully submitted that in an obviousness rejection, the prior art need only *suggest* the instant invention. In instant case, Chen is generally directed to a controlled release device for a once-a-day administration for water-insoluble drugs including the instant HMG-CoA Reductase Inhibitors, to increase patient compliance. See column 2, lines 42-65.

> **Various medicaments may be administered using the osmotic tablet of the present invention.** These medicaments include medicaments which are water soluble to practically insoluble in water. The term practically insoluble is used to include those substances which are soluble at a level of 1 part of solute to from 100 to more than 10,000 parts of water per part of solute. The term water soluble includes those substances which are soluble at level of one part of solute to 5 parts of water or less.
>
> Examples of categories of water insoluble medicaments which may be utilized, at therapeutic dose levels, in the controlled release tablets of the invention include anti-hypertensives, calcium channel blockers, analgesics, anti-neoplastic agents, anti-microbials, anti-malarials, non-steroidal anti-inflammatory agents, diuretics, anti-arrythmia agents, hypoglycemic agents and the like. Specific examples of medicaments include nifedipine, nisoldipine, nicardipine, nilvadipine, felodipine, bendroflumethazide, acetazolamide, methazolamide, chlorpropamide, methotrexate, allopurinol, erythromycin, hydrocortisone, triamcinolone,

> prednisone, prednisolone, norgestrel, norethindone, progesterone, norgesterone, ibuprofen, atenolol, timolol, cimetidine, clonidine, diclofenac, glipizide, **lovastatin, fluvastatin, simvastatin, pravastatin,** fexofenadine, and the like. Useful water-soluble medicaments include various therapeutic agents such as decongestants, antihistamines, analgesics, sedatives, anti-inflammatory, anti-depressants, antihypertensives and the like at therapeutic dosage levels.

Although the pharmacokinetics of nifedipine are exemplified, a skilled artisan one would have been motivated to substitute nifedipine with the instant lovastatin and expect similar pharmacokinetic values since Chen clearly suggests the use of other drugs in place of nifedipine. It is respectfully submitted that that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971). Thus, the examiner respectfully submits that Chen et al do not need to exemplify every single drug taught to be suitable in order to render the instant invention *prima facie* obvious.

With regard to Appellant's argument that the exemplified release of nifedipine will not extend to the instant lovastatin, fluvastatin, simvastatin, and pravastatin (HMG-CoA Reductase Inhibitors), the examiner respectfully points out that Chen et al teach the *general* mechanism of the controlled release device irrespective of the medicament utilized. Note column 3, lines 45-67.

> It is believed that as water passes through the membrane on the surface of the tablet of the invention, the core swells and increases the pressure inside the tablet. This causes a very slight expansion of the partially hydrated core which is controlled by the use of a relatively small amount of the water swellable polymer.
>
> The expansion of the core will cause the membrane to open to relieve the internal pressure. Once the initial opening or openings are formed, the swelling effect of the core components will cause the contents of the core to extrude through the initial opening without complete disintegration of the membrane. The internal pressure which is exerted on the membrane by the swelling and expanding osmotic core is relieved by the passage of the first portions of the core contents through the initial openings. This effect is unexpected because it could not have been predicted that small, randomly formed openings in the membrane would form and relieve the internal pressure by gradually controlled release than dose dumping the entire core contents by a bursting or disintegration of the membrane. It is believed that the formation of the small openings, without initial loss of the integrity of the rest of the membrane by uncontrolled expansion of the osmotic core, is responsible for the 24 hour therapeutic blood level which is achieved by the controlled release tablet of the invention.

Thus, the novelty of Chen's controlled device is not the medicament used per se and rather the ability of the controlled release device in maintaining the therapeutic blood serum levels of the medicament over 24 hours. Therefore, it is the examiner's position that a skilled artisan would *reasonably* expect that Chen's controlled release dosage form would function the same irrespective of the drug utilized. Again appellant has not provided any evidence to the contrary. Further, it is noted that both nifedipine and HMG-CoA Reductase Inhibitors such as lovastatin are water-insoluble. Thus, a question of drug solubility factors effecting the release of rate do not arise.

Appellant argues that the size of the genus is not sufficiently small as to render the each member inherently disclosed. Appellant argues that Chen does not provide any motivation to select lovastatin.

Firstly, the examiner respectfully submits that Appellant's arguments with regard to genus-species is not relevant to the instant rejection since the rejection has not made under an anticipation and rather, the rejection is made under obviousness. Thus a skilled artisan need not "immediately envisage" the use of lovastatin in the dosage form since this is a requisite for anticipation and not obviousness. The examiner has not purported that a skilled artisan would immediately envisage the use of lovastatin, rather the examiner's position is that it is obvious to use lovastatin since Chen teaches lovastatin as a suitable drug to use in the controlled release dosage form. Therefore, the motivation of utilizing lovastatin is within the disclosure of Chen itself. The examiner points out that the selection of a drug is *prima facie* obviousness depending on the disease to be treated. Thus, a skilled artisan would have been motivated to select

lovastatin, fluvastatin, simvastatin, and pravastatin, from the drugs taught by Chen et al, to treat cholesterol levels.

Appellant argues that "If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species."

As set forth in the rejection, Chen on column 2, lines 50-67 teaches,

> Examples of categories of **water insoluble medicaments which may be utilized**, at therapeutic dose levels, in the controlled release tablets of the invention include anti-hypertensives, calcium channel blockers, analgesics, anti-neoplastic agents, anti-microbials, anti-malarials, non-steroidal anti-inflammatory agents, diuretics, anti-arrythmia agents, hypoglycemic agents and the like. Specific examples of medicaments include nifedipine, nisoldipine, nicardipine, nilvadipine, felodipine, bendroflumethazide, acetazolamide, methazolamide, chlorpropamide, methotrexate, allopurinol, erythromycin, hydrocortisone, triamcinolone, prednisone, prednisolone, norgestrel, norethindone, progesterone, norgesterone, ibuprofen, atenolol, timolol, cimetidine, clonidine, diclofenac, glipizide, **lovastatin, fluvastatin, simvastatin, pravastatin,** fexofenadine, and the like. Useful water-soluble medicaments include various therapeutic agents such as decongestants, antihistamines, analgesics, sedatives, anti-inflammatory, anti-depressants, antihypertensives and the like at therapeutic dosage levels.

Moreover, the examiner also relies on Cheng et al to provide the motivation of specifically selecting lovastatin, a HMG-CoA Reductase Inhibitor. As discussed in the rejection, a skilled artisan would have been motivated to select lovastatin specifically with a *reasonable* expectation of success and similar results since Chen et al suggest medicaments including lovastatin and Cheng teaches lovastatin is an effective drug in reducing cholesterol serum levels in humans and it is beneficial to utilize *a controlled or sustained release device*. Summarily, if one desired reducing cholesterol levels, one would specifically select lovastatin as the drug of choice. Lastly, it is noted that Cheng teaches a controlled release device (CRS14) formulation providing a **Tmax of 7.5 + 1.2 hours (standard deviation 8.7 hours and Appellant claims about 10 hours)** for an 80mg lovastatin oral dose. Thus, one would have been motivated to specifically formulate a lovastatin controlled release device utilizing Chen's inventive controlled

release device since Cheng teaches a controlled release device that sustains the concentrations of the HMG-CoA reductase inhibitors results in a better therapeutic efficacy and Chen teaches a controlled release device that maintains the blood serum, level of the medicament over 24 hours.

Appellant argues that nifedipine and lovastatin are not structurally similar. Appellant argues that Chen does not provides any teaching of compression forces, temperature, humidity processing parameters. Therefore, Appellant argues that formulation of a controlled release device comprising an alkyl ester of hydroxy substituted naphthalene in accordance with the teachings of Chen et al. to achieve the claimed Tmax parameters, such formulation "would be a result of optimization of conditions".

Firstly, the examiner has not purported there is a structural similarity with nifedipine and lovastatin. The examiner notes the difference in pharmacological effects and the structure of the compounds and the only shared property is that both are water-insoluble compounds. However, the premise of the rejection is not that one would expect similar results since nifedipine and the instant alkyl esters of hydroxyl substituted naphthalenes are structurally or functionally the same. The premise is that that Chen's controlled release device is substantially similar, if not same, to the instantly claimed controlled device as discussed above. Thus, the prior art's controlled release device will meet the instantly claimed functional limitations, i.e. the claimed Tmax parameters.

Secondly, the examiner respectfully submits that the instant claims are directed to a product, i.e. a controlled release device, and not a process of making a controlled release device. The examiner recognizes that each drug has its own physical characteristics and this must be given consideration when formulating the dosage form. However, Chen's inventive thrust lies

not in the medicament utilized but in the controlled release formulation and maintaining the therapeutic serum levels of the medicament. Chen et al teach a *general* method of formulating a controlled release device that maintains the therapeutic serum levels of the medicament, which may be applied to the any medicament that is "water soluble to practically insoluble in water" as defined on column 3. This includes lovastatin, fluvastatin, simvastatin, and pravastatin. Note column 3, lines 28-50.

> The medicament, the pharmaceutically acceptable water soluble polymer binder and the water soluble osmotic agent are first formed into a granulation which is subsequently blended with a water swellable osmotic polymer and suitable excipients to form a composition which may be compressed into tablets. In the alternative, the water soluble pharmaceutically acceptable polymer may be combined with the medicament and the water soluble osmotic compound and the water swellable osmotic polymer. After a granulation is formed from this blend, the granules may be tabletted with or without the addition of an additional quantity of a water soluble compound and/or the water swellable osmotic polymer. A tabletting machine is used to compress the granulation mixture into a core tablet having a homogeneous core. The homogeneous core is subsequently completely coated with a modified polymeric membrane to form the controlled release tablet of the invention.

Again it is pointed out that Chen generally teaches a controlled release device that provides controlled release of a water-insoluble medicaments, *in general,* with the purpose of maintaining the serum levels. Therefore, there is ***reasonable*** expectation that the pharmacokinetics provided by the controlled release device would remain the same regardless of the drug utilized, i.e. the substitution of exemplified water-insoluble nifedipine with water-insoluble lovastatin. It is further pointed out that the instant rejection is made under obviousness and optimization is not inventive in view of the guidance provided by the prior art. As clearly acknowledged by applicant, when formulating the dosage form comprising hydroxy substituted naphthalene, one would optimize the conditions to obtain the dosage form. Assuming *arguendo* that one needs to optimize the conditions, the examiner points respectfully points out that optimization via routine experimentation is not an indication of unexpectedness.

For the forgoing reasons, it is the examiner's position that Chen et al renders the instant invention *prima facie* obvious.

C) Claims 1-13, 18, 19, 21, 22, 25-47, 76-77, and 80 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 6,485,748 in view of Remington's Pharmaceutical Science (18th edition, 1990).

Appellant argues " when considering when the invention defined in the claim of an application is an obvious variation of the invention defined in the claims of a patent, the disclosure of the patent may not be used as prior art. However, the specification can be used as a dictionary to learn the meaning of a term in the patent claim, or be examined with respect to those portions which provide support for the claims (See MPEP 8th Edition, Revision 2, Section 804(2)(B)(1))" Appellant argues that US 6,485,748 et al fail to teach, suggest, or hint the Tmax range recited in the instant claims. Appellant argues there are no dependent claims directed to HMG CoA reductase inhibitors. Appellant argues there is no statement in either the specification or the claims of the '748 patent relating to Tmax, or suggestion that the in-vivo plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing the class drugs known as alkyl esters of hydroxy substituted napthalenes.

Appellant's arguments are not persuasive for the following reasons:

As acknowledged by Appellant "the specification can be used as a dictionary to learn the meaning of a term in the patent claim, or be examined with respect to those portions which provide support for the claims." US'748 claims the same structure as disclosed by Appellant on

Table 1, page 19 of the instant specification. Further, US '748 claims the medicament is a slightly to practically insoluble in water at 25 degrees Celsius. The specification of US '748 defines lovastatin as a drug that falls into this definition. Thus, the examiner is not utilizing the disclosure of US '748 and rather relies on US '748's disclosure to *define* a term. The difference between the instant application and US '748 is that the instant application claims the controlled release device in terms of function and US '748 claims the same controlled release device in structural terms. However, similar scopes are claimed, albeit in a different manner. Although US '748 does not claim the Tmax provided by the controlled release device, the examiner respectfully submits that claiming a functional limitation of a product does not change the product itself since the same product is claimed. Thus, it is respectfully submitted that the instant product and US patent are obvious over each other.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Sharmila G. Landau

10/22/07

Conferees:

Michael Hartley

Sreenivasan Padmanabhan

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER